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# Mathematical Model of the Hydrotropic Microwave Assisted Extraction of Anti Malarial Agent from *Andrographis Paniculata*

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**Abstract**

The drugs traditionally used to treat uncomplicated malaria have become ineffective, due to the development of drug resistance. It has led to a widespread promotion of artemisinin-based combination therapy (ACT) as a strategy for effective management of *Plasmodium falciparum* malaria. The main drawback of the ACTs is their high cost. Hence, many phytoconstituents are currently investigated for their antimalarial activity. One of them is andrographolide of *Andrographis paniculata* (Burm.f.) Wall. A combination of microwave assisted-extraction and the utilization of hydrotrope as the extraction medium is already proved as a potential safe alternative for the separation of andrographolide. Mathematical models of extraction plays a crucial role in basic research of phytoconstituent separation; they are not yet available for hydrotropic-microwave assisted extraction of andrographolide. Therefore, there is a need to conduct a scientific study in this field. The mathematical model is a useful engineering tool for equipment optimization, simulation, design and control, allowing theoretical description of the process and evaluation of the kinetic constant. The aim of this work was to model the kinetics of hydrotropic-microwave assisted extraction of andrographolide. The kinetics of hydrotropic-microwave assisted extraction of andrographolide was studied for two different powers of the microwave extractor (10 % and 30 %). A second order kinetic model describes the solid liquid extraction process of andrographolide from *Andrographis paniculata* (Burm.f.) Wall.



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*Keywords*: Andrographolide; hydrotropic; kinetic; microwave assisted extraction

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**Nomenclature**

| | |
|---|---|
| **Cs** | extraction capacity (concentration of solute at saturation in $g \cdot L^{-1}$) |
| **Ct** | concentration of solute in the suspension at time t |
| **h** | initial reaction rate ($g \cdot L^{-1} \cdot min^{-1}$) |
| **k** | second-order extraction rate constant ($L \cdot g^{-1} \cdot min^{-1}$) |
| **min** | minute |
| **t** | time (minute) |

## 1. Introduction

The development of drug resistance in the malaria treatment has led to a widespread promotion of artemisinin-based combination therapy (ACT) as a strategy for effective management of *Plasmodium falciparum* malaria. World Health Organization (WHO) has, since 2001, recommended that malaria endemic countries change their treatment policies and adopt combination therapy, and in particular artemisinin-based combination therapy as the first- line antimalarial treatment[1].

The ACTs combine an artemisinin-derivative (a relatively new group of drugs which are very effective) with another longer-lasting drug to attempt to reduce the risk of further resistance developing. The ACTs used include artemether-lumefantrine; artesunate-amodiaquine; artesunate sulfadoxine-pyrimethamine; and artesunate mefloquine-cloroquin[2,3].

The ACTs were shown to be more effective and seem to be relatively safe with few serious side-effects. The main drawback of the ACTs is their high cost. Hence, many phytoconstituents are currently investigated for their antimalarial activity. One of them is andrographolide of *Andrographis paniculata* (Burm.f.) Wall.

*Andrographis paniculata* (Burm.f.) Wall is a plant that has been effectively used in traditional Asian medicines for centuries. *Andrographis paniculata* (Burm.f.) Wall is known as an immune system booster, used in fever and dispel toxins from the body[4,5]. This herb has been valued for treating infectious diseases and is highly regarded as having preventive effects against ailments such as liver damage, hyperglycaemia, dysentery, cancer, pulmonary tuberculosis, acute and common cold. The therapeutic activity of this plant is attributed to the major phytoconstituents of the plant, a diterpenic lactone compound known as andrographolide, and related diterpenes[6].

Andrographolide has been reported to have diverse pharmacological potentials including antiviral, anti-inflammatory, anticancer, antimicrobial, antimalarial, antihypertensives, antidiabetics, and antifilarial activities[6-8].

As an antimalaria agent, andrographolide has been evaluated for its efficacy. In combination with curcumin, it exhibits potent anti-malarial activity for novel combinatorial drug therapy against drug-resistant malaria[3].

Phytoconstituents separation through solid liquid extraction is a widely used process in pharmaceutics. Consequently, many authors have studied different extraction methods.

Conventional methods employed in the andrographolide extraction were reported as effective, but also as the cause for thermal degradation of heat sensitive compounds[3] including andrographolide, they also leave traces of toxic solvents in the solute[6,9,10].

Combination of microwave assisted-extraction and the utilization of hydrotrope as the extraction medium are already proved as potential alternatives for the separation of andrographolide. Hydrotropes are proved to be a safe medium for microwave assisted extraction of andrographolide. Hydrotropes were also proved to increase the solubility of slightly water soluble androgpraholide. Compared to urea and sodium acetate, sodium benzoate is more suitable in the androgpraholide microwave assisted extraction[11].

Mathematical models of hydrotropic-microwave assisted extraction of andrographolide are not available yet. Mathematical models of extraction play a crucial role in the industry of phytoconstituent separation, and are a useful engineering tool for equipment optimization, simulation, design and control, allowing theoretical description of the process and evaluation of kinetic constants. The aim of this work was to examine the mathematical model, which was the kinetics of hydrotropic-microwave assisted extraction of andrographolide.

## 2. Material and methods

### *2.1. Raw material and chemicals*

The aerial parts of Andrographis paniculata (Burm.f.) Wall were harvested after fruiting and collected from local plantation in Gunungpati, Semarang, Central Java. The aerial parts include stems, leaves, flowers, and fruits. Chemical used was sodium benzoate (Sigma-Aldrich, 99 %) which was purchased from CV. Damai Sejahtera Prima.

### *2.2. Apparatus*

Hydrotropic-microwave assisted extraction was conducted in a modified domestic microwave oven. The microwave was modified and equipped with extraction flask and a spiral condenser.

Fig.1. Modified microwave extractor

### *2.3. Extraction*

Aerial parts of *Andrographis paniculata* (Burm.f.) Wall were collected, dried and ground into powder. Twenty grams of dried powder was subjected to 200 mL of hydrotrope solution. The hydrotrope used was 2M of sodium benzoat. The mixture was placed in a 500 mL round bottom flask and extracted in the modified microwave extractor at system powers of 39.9 W and 119.7 W. Samples were taken at time intervals of 2.5 min, allowed to stand for 1 h, and then filtered. The residue was washed with demineralised water, and then an equal volume of demineralised water was added. The extract was then centrifuged for 15 min at 4000 × *g*, dried and weighed.

### *2.4. Kinetic model*

Various models of solid liquid extraction process have been desrcibed[12,13]. Garkal et al.[13] shows, in the study of the mechanisms and kinetics in the extraction process of eugenol from leaves of *Ocimum Sanctum* Linn (Tulsi), that a model based on a second-order extraction kinetics was the most suitable model for a solid–liquid extraction process. It was then possible to build the kinetic models of a solid–liquid extraction and the extraction order and rate constant remained to be determined by experiments.

According to a second-order rate law, Sayyar, et al.[14] described the rate of dissolution for the solute contained in the solid from plant cells to solution by Eq (1):

$$\frac{dC_t}{dt} = k(C_s - C_t) \quad (1)$$

Where k is the second-order extraction rate constant (L · $g^{-1}$ · $min^{-1}$), Cs the extraction capacity (concentration of solute at saturation in mg · $L^{-1}$) and Ct is the concentration of solute in the suspension at time t (min). By considering the initial and boundary conditions, t=0 to t and Ct =0 to Ct, the integrated rate law for a second-order extraction was obtained:

$$C_t = \frac{k.t.C_s^2}{1 + k.t.C_s} \quad (2)$$

By transforming Eq. (2), a linear form shown in Eq. (3) can be obtained and the extraction rate can be written as Eq (4).

$$\frac{1}{C_t} = \frac{1}{kC_s^2} + \frac{t}{C_s} \quad (3)$$

$$\mathrm{h} = \frac{C_t}{t} = \frac{1}{1/kC_s^2) + (t/C_s)} \quad (4)$$

The initial extraction rate, h, when t approaches 0, can be defined as:

$$h = kC_s^2 \quad (5)$$

and, the concentration of solute at any time can be expressed after rearrangement as:

$$C_t = \frac{t}{\frac{1}{h} + \frac{t}{C_s}} \quad (6)$$

The initial extraction rate, h, the extraction capacity, Cs, and the second-order extraction rate constant, k, can be determined experimentally from the slope and intercepted by plotting t/Ct versus t.

## 3. Result and discussion

Second order kinetic model was used to describe the solid liquid extraction process of andrographolide from *Andrographis paniculata* (Burm.f.) Wall. The kinetics of hydrotropic-microwave assisted extraction of andrographolide from *Andrographis paniculata* (Burm.f.) Wall was studied at two different powers of the microwave extractor (10 % and 30 %).

At 30 % microwave power (119.7 W), the concentration of solute in the suspension increased with time of extraction until it reached plateau or constant after 5 min of extraction, corresponding to solute concentration of 0.035 g · $L^{-1}$ (Fig. 2). It was the highest concentration of solute that was achieved at 5 min of extraction at 30 % of power level. Meanwhile at 17.5 min of extraction time, the solute concentration of the extraction conducted at 10 % power was higher (0.040 5 g · $L^{-1}$ ).

Possibly, the application of higher microwave power has led to the thermal degradation of the phytoconstituent, thereby lowering the hydrotropic-microwave assisted extraction capacity of andrographolide. Microwave power and temperature are interrelated because high microwave power can increase the temperature of the system. On the application of 30 % and 10 % microwave power, the final temperature was up to 70 °C and 40 °C, respectively.

The extraction rate is fast at the beginning and slow towards the end of the extraction process. Changes of solute concentration in the liquid phase affected the mass transfer of extraction process. At the first stage, andrographolide concentration was low. Thus, andrographolide diffuses rapidly from solute to liquid phase. Diffusion rate decreased as the time of extraction increased due to the high solute concentration in liquid at the second stage. Although the extraction time increased after the maximum andrographolide was extracted, it did not show any changes or

significance in amount of andrographolidel extracted. This finding confirms the second-order model kinetic study of androgapholide extraction[14].

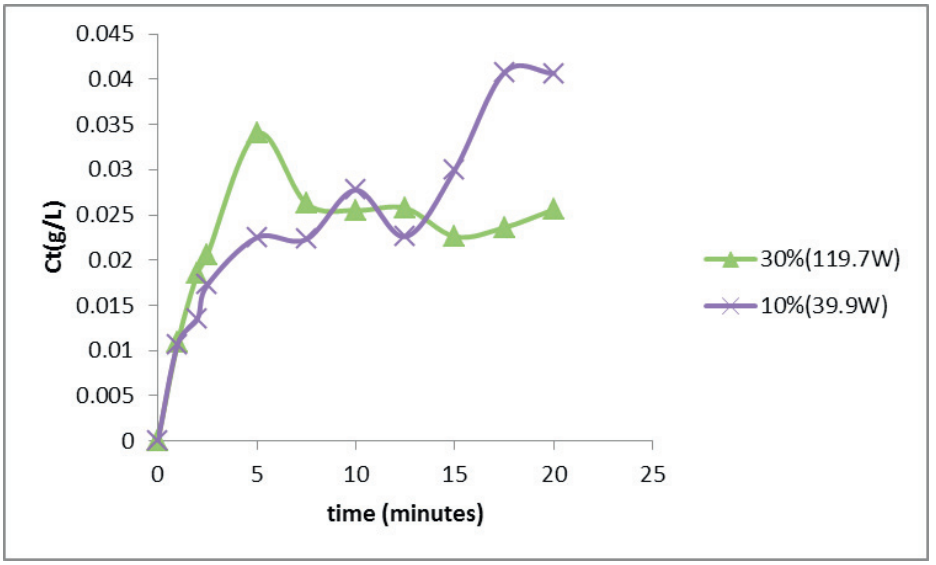


Fig. 2. Extraction kinetics at differrent microwave power

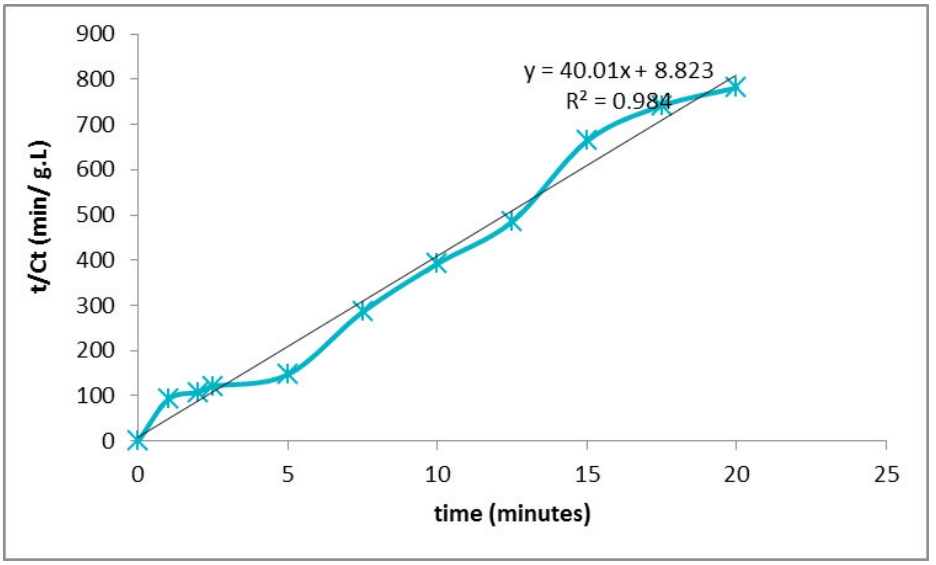


Fig. 3. Plot t vs t/Ct of hydrotropic microwave assisted extraction conducted at 119.7 W (30 % of microwave maximum power)

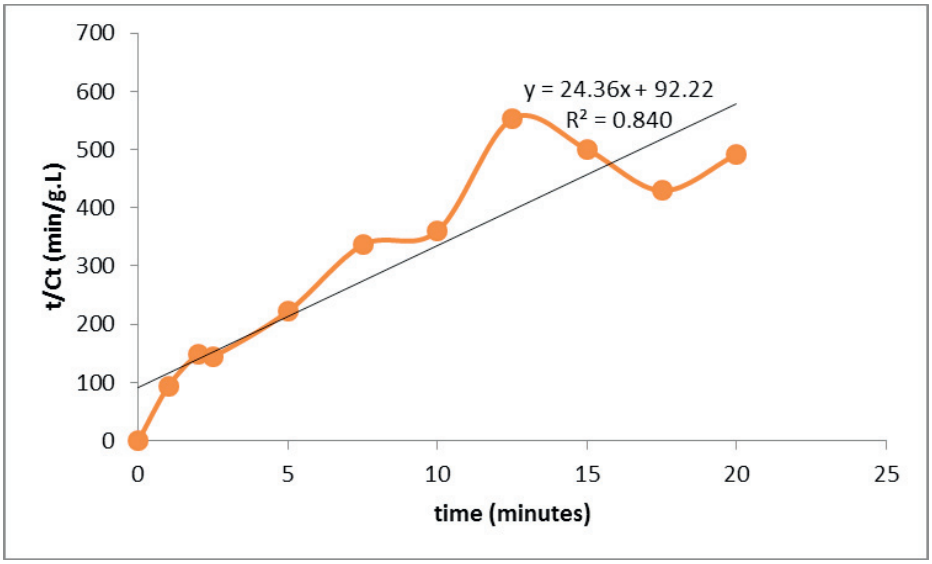


Fig 4. Plot t vs t/Ct of hydrotropic microwave assisted extraction conducted at 39.9 W (10 % of microwave maximum power)

The experimental result was then plotted using a second-order model by plotting t/Ct versus t. The initial extraction rate (h), the extraction capacity (Cs), the second order extraction constant (k) and coefficient of determination (R2) were calculated experimentally by referring to the linear plot in Fig. 3 and Fig. 4.

Table 1. Kinetics constant for hydrotropic-microwave assisted extraction of andrographolide

| Power | $C_s$ (g · $L^{-1}$) | k (L · $g^{-1}$ · $min^{-1}$) | h (g · $L^{-1}$ · $min^{-1}$) | $R^2$ |
|---|---|---|---|---|
| 30 % | 0.024 | 181.43 | 0.11 | 0.984 |
| 10 % | 0.041 | 6.43 | 0.01 | 0.840 |

The results show that the value of the regression coefficient (R2) lies between 0.84 to 0.98. This indicates that the data, especially the extraction that was conducted at power level of 30 % (119.7 W), are well described by second order kinetics. Meanwhile based on the graphic plot of t vs t/Ct of the hydrotropic microwave assisted extraction that was conducted at power level of 10 % ( (39.9 W), seems that the simple second order kinetic model is interfered. It might be due to the utilization of all aerial parts of the *Andrographis paniculata* (Burm.f.) Wall. There may be parts/compartments that are more readily extractable than others. It is found that the andrographolide of *Andrographis paniculata* (Burm.f.) Wall leaves is three times higher in amount and more readily extractable than the andrographolide found in *Andrographis paniculata* (Burm.f.) Wall stem[7]. Furthermore, from graph t/Ct versus time, the slope is equal to 1/Cs and intercept is equal to $1/kCs^2$. The data is shown in Table 1.

## 4. Conclusion

The second order kinetics model is proved and fits the hydrotropic-microwave assisted extraction of andrographolide from *Andrographis paniculata* (Burm.f.) Wall.

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